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<p>(54) Title: <b>METHOD OF OPHTHALMIC DRUG DELIVERY</b></p> <p>(57) Abstract</p> <p>A method for prolonged delivery of a therapeutic agent to the eye is disclosed. The method provides for the addition of a desired drug to a suitable, preferably non-aqueous, carrier. An amount of the carrier containing the therapeutic dose of the drug is placed on the skin exterior to the ocular surface near the lateral and lower lid margins. Movements of the orbicularis oculi associated with the scissor-like closing of the lids of the eye continuously transport small portions of the therapeutic agent and carrier into the interpalpebral space where the drug is released to the corneal surface. Further provided is a calcium-based ophthalmic composition which is particularly effective in treating dry eye syndrome and which is optimally delivered by the method just described.</p>			

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## METHOD OF OPHTHALMIC DRUG DELIVERY

5        The present application is a continuation-in-part of United States Patent Application Serial Number 07/926,244, filed August 6, 1992.

### Field of the Invention

10      This invention relates generally to the treatment of diseases of the human eye and more particularly to methods of delivering drugs and other agents to the eye for treating various eye diseases.

### References

15      Dohlman. 1971. Trans. Ophthal. Soc. U.K. 91:105.

Huth et al. 1981. Arch. Ophthal. 99:1628.

Lamberts. 1980. International Ophthalmology Clinics 20 (3):63.

Lemp. 1972. Annals of Ophthalmology 4:15.

20      Lemp. 1973. International Ophthalmology Clinics 13:1345.

MacKeen. 1980. International Ophthalmology Clinics 20(3):79.

Pavan-Langston. 1973. International Ophthalmology Clinics 13:231.

### Background of the Invention

Treatment of diseases of the human eye is often accomplished through the topical administration of therapeutic agents. Any topical method of drug delivery must take into account and attempt to overcome many inherent physiological systems that operate to protect and maintain the vital front

surfaces of the eye. For example, the cornea and conjunctiva are coated with mucin and bathed in a complex aqueous fluid derived mainly from the lacrimal glands. The region between the lids of the normal eye -- the interpalpebral space -- is 5 covered by the preocular tear film, a very thin (generally less than 40 $\mu$ M) liquid layer covering the cornea and conjunctiva. The preocular tear film is provided on its anterior surface with a thin film of lipids derived from the Meibomian glands that open along the lid margin. Because the tear film is dynamic and 10 subject contamination, the tear film is continually replaced, the effete tear residues being forced from the eye through the pair of puncta and associated canaliculi at the medial corner of the eye by blinking.

In order to have therapeutic effect, a drug or other 15 compound must generally pass into the eye through the cornea. Problematic to topical delivery of drugs is in fact that the cornea is less permeable than the conjunctiva. Further, the surface area of the conjunctiva is highly vascularized, and its surface area is some 14 times greater than the surface area of the cornea. For 20 these reasons, the transconjunctival loss of instilled drugs is considerable. Further, water soluble drugs are quickly eliminated from the eye surface through tear outflow, a process that is often accelerated in the diseased eye, and topical 25 delivery of drugs to the eye in sufficient quantity and for sufficient periods is often difficult. Thus, the effectiveness of prior art methods of topical drug application is often limited.

The most common known topical delivery of ophthalmic drugs is accomplished using water-based compositions, either 30 as a solution or a suspension. Such compositions are generally delivered as drops or as a wash directly to the eye surface. Because such aqueous compositions are quickly eliminated from the eye, various attempts have been made to enhance the

contact time and/or drug delivery characteristics by employing a variety of water-soluble polymers, both synthetic and natural.

For stability, these water-polymer preparations must contain a preservation system when intended for a multiple dose use.

- 5      Further, most compositions must be buffered, usually to an acidic range. Examples of stabilized solutions and tear substitutes are disclosed in U.S. Patent 4,407,791 to Stark; 4,409,205 to Shively; and 5,075,104 to Gressel et al. When instilled in the eye, the drug preparation usually overwhelms the  
10     resident tear volume, resulting in an initial loss both of some drug and the resident tear constituents. Further, the relatively cool temperature and acidic pH of the drug preparation produces a strong blink reflex coupled with reflex tearing, thereby resulting in further loss of the drug preparation from the  
15     eye surface by outflow.

Although the use of aqueous vehicles is a common and widespread means of topical delivery, the use of such a delivery system has resulted in a number of problems. First, the very nature of the delivery system, in particular its aqueous and

- 20     irritating characteristics, results in a rapid loss of drug from the eye, necessitating frequent and repetitive reintroduction of the drug-bearing composition to the eye. This is not only inconvenient to the patient, but results in less efficacious treatment because of the difficulty in maintaining a more or less continuous delivery of drug through the cornea to the eye. This difficulty of delivery is further compounded by the loss of drug preparation across the larger and more permeable vascular conjunctival surface. Preservatives and stabilizing compounds can also result in tissue damage to the cornea and conjunctiva.  
25

- 30     In attempts to avoid the problems associated with aqueous drug delivery, suspensions of insoluble drug preparation have been used, resulting in longer drug action

through the slow dissolution of particles trapped in the cul de sacs. However, the use of ophthalmic suspensions has its own set of problems, primarily inaccurate dosages due to inadequate patient resuspension.

5        Water-insoluble ointments have also been used as vehicles for drug delivery. However, the use of ointments has many attendant problems, not the least of which is discomfort and loss of visual acuity due to the excessively thick and uneven layer produced by the ointment on the cornea. In  
10      addition, ointments are difficult to apply since the delivery method requires application of the ointment to the tarsal conjunctiva of the exerted lower lid.

In addition to purely fluid vehicles, such as aqueous solutions, suspensions and ointments, solid vehicles in the form  
15      of drug-releasing inserts have also been utilized to deliver drugs to the eye surface. Many of these devices and methods are discussed in Pavan-Langston (1973). Examples of such inserts include the PVA inserts of Maichuk and the Ocuserts<sup>TM</sup> of Alza.  
20      Some inserts are hydrophilic contact lenses that have been impregnated with a drug that is released to the corneal surface over time after lens insertion. In other cases, the insert actually dissolves slowly to release the drug. The use of inserts however is problematic. They are cumbersome, increase the risk of eye infection by agents carried into the eye on the insert,  
25      and are expensive. Further, it is not clear that inserts actually achieve as high or as prolonged a delivery of drug as is sometimes claimed. For example, much of the drug released from an insert is still likely to be taken up by the conjunctiva and pass thereafter into the general circulation with little or no therapeutic benefit for the eye. Further, the irritation resulting  
30      from the use of the insert probably results in increased flow of lacrimal fluid, thereby increasing the likelihood that the drug will

be washed out of the eye.

A significant problem associated with all known methods of topical drug delivery stems from the muscular coordination required of the patient for self-application. Both soluble aqueous vehicles and aqueous suspensions are generally delivered through drops to the eye. Ointments require precise delivery to the inside portion on an eyelid, while ocular inserts of various types require finger delivery of an object into the eye. Each of these manipulations can be especially difficult for the elderly and can result in serious injury to the eye when the drug is delivered to the eye with too much force.

One ophthalmological disease that has proved especially susceptible to treatment by the method just described is dry eye, (also known as keratoconjunctivitis sicca), is a common ophthalmological disorder affecting millions of Americans each year. The condition is particularly widespread among post-menopausal women due to hormonal changes following the cessation of fertility. It is one of the most common of human eye diseases and is generally treated through the topical delivery of a variety of therapeutic agents.

Dry eye may afflict an individual in varying severity. In mild cases, a patient may experience burning, a feeling of dryness, and persistent irritation when debris lodge between the eye lid and the eye surface. In severe cases, vision may be substantially impaired. Good reviews of dry eye syndrome and standard methods of treatment may be found in Dohlman (1971) and Lemp (1973).

Although it appears that dry eye may result from a number of unrelated pathogenic causes, all presentations of the syndrome share a common effect, the breakdown of the pre-ocular tear film, which results in dehydration of the exposed outer surface and many of symptoms outlined above.

Practitioners have taken several approaches to the treatment of dry eye. One common approach has been to supplement and stabilize the preocular tear film using so-called artificial tears. Another approach has been the use of ocular 5 inserts that function variously to provide a tear substitute or to stimulate endogenous tears.

Examples of the tear substitution approach include the use of buffered, isotonic saline solutions, aqueous solutions containing water soluble polymers that render the solutions 10 more viscous and thus less easily shed by the eye. Tear reconstitution is also attempted by providing one or more components of the tear film such as phospholipids. Examples of these treatment approaches are disclosed in United States Patents 4,131,651 to Shah et al.; 4,370,325 to Packman; 15 4,409,205 to Shiverly; 4,744,980 and 4,883,658, both to Holly; 4,914,088 to Glonek; and 5,057,104 to Gressel et al.

United States Patents directed to the use of ocular inserts in the treatment of dry eye include 3,991,759 to Urquhart. The use of ocular inserts is also discussed in detail in Lamberts 20 (1980).

Another recent approach involves the provision of lubricating substances in lieu of artificial tears. United States Patent 4,818,537 to Guo discloses the use of a lubrication, liposome-based composition. United States Patent 4,966,773 discloses the use of microfine particles of one or more retinoid. 25

Aside from the above efforts, which are directed primarily to the alleviation of symptoms associated with dry eye, also known are methods and compositions directed to treatment of the dry eye condition. For example, United States Patent 30 5,041,434, discloses the use of sex steroids, such as conjugated estrogens, to treat dry eye condition in post-menopausal women.

Although these approaches have met with some success, problems in the treatment of dry eye nevertheless remain. The use of tear substitutes, while temporarily effective, generally requires repeated application over the course of a patient's 5 waking hours. It is not uncommon for a patient to have to apply artificial tear solution ten to twenty times over the course of the day. Such an undertaking is cumbersome and time consuming, increases the exposure of the eye to preservative agents and can be very expensive.

10       The use of ocular inserts is problematic. Aside from cost, they are often unwieldy and uncomfortable. Further, as foreign bodies, they pose a risk of acting as a vector for infectious organisms. In situations where the insert does not itself produce and deliver a tear film, artificial tears must still be 15 delivered on a regular and frequent basis. Indeed, Pavan-Langston (1973) has concluded that, as a rule, ocular inserts are not very effective in the treatment of many dry eye conditions.

20       In view of the foregoing, there is a clear need for a reliable, effective, method of topical delivery of therapeutic agent to the cornea that is both easy to administer and long acting.

#### Summary of the Invention

25       It is an object of the invention to provide an easy to administer method of topical delivery of a drug or therapeutic agent to the human eye.

30       It is yet another object of the invention to provide a method of ophthalmic drug delivery that is capable of delivering doses of a drug to the cornea of the human eye over a prolonged period.

It is another object of the invention to provide a method

of extraocular ophthalmic drug deliver.

Still another object of the invention is to provide a method of topical ophthalmic drug delivery that significantly lessens the risk of injury to the eye.

5 Still another object of the invention is to provide a method of ophthalmic drug delivery this is highly cost effective.

A further object of the invention is to provide a topical method for delivering a drug or other composition for the treatment of dry eye syndrome.

10 It is yet another object of the invention to provide a composition for the treatment of dry eye that is easy and convenient to administer.

15 Yet another object of the invention is to provide a composition for the treatment of dry eye that does not require continual or even frequent delivery to the eye in order to be effective.

A further object of the invention is to provide a composition for treating dry eye that is inexpensive.

20 Still another object of the present invention is to provide a method for utilizing the composition of the invention in the treatment of dry eye syndrome.

25 The invention meets these objects by an easy to administer, long-acting composition capable of delivering a desired amount of a drug or other therapeutic agent to the cornea of the eye. According to the method of the invention, a desired drug or other compound is mixed with a pharmacologically acceptable carrier to form a desired ophthalmological composition. The carrier is preferably hydrophobic in nature. The composition is then delivered 30 manually or by sterile cotton application to extraocular skin adjacent to the lateral canthus of the eye. Movements of the orbicularis oculi associated with the scissor-like closing of the

lids of the eye continuously transport small portions of the composition into the eye where the drug is released to the cornea and treatment effected.

According to another aspect of the invention, the objects  
5 regarding the treatment of dry eye syndrome are met by providing a minimal water-soluble, calcium based composition that is delivered in an appropriate vehicle to the eye according to the delivery method of the invention just described. Calcium in this composition is present as a more or less water insoluble  
10 salt, such as calcium carbonate.. The calcium salt is very finely divided into particles, preferably in micronized form. The finely divide calcium salt is then dispersed in a pharmacologically acceptable carrier, preferably hydrophobic in character.

It has been discovered that a preferably hydrophobic drug  
15 containing vehicle delivered to extraocular skin adjacent to the lateral canthus of the eye will be taken up by and communicated across the surface of the human eye as a result of the scissoring motions of the eye lid during blinking. this method effect the slow and more or less continuous delivery of  
20 a desired drug to the eye surface, and ultimately through the cornea and into the eye. The nature of the ophthalmological composition combined with the continuous delivery ensures that a fairly constant amount of the desired therapeutically agent is present in the tear film and in contact with the cornea for a  
25 prolonged period. This method is clearly advantageous over the prior art in that continuous delivery of therapeutically efficacious amounts of a desired drug can be delivered over prolonged periods. The method avoids the comfort and visual acuity problems associated with ointments and inserts and greatly  
30 lessens the likelihood of injury to the eye in that the ophthalmological composition is not delivered directly to the eye surface. This minimizes system loss of drug across the

conjunctiva, maximizing corneal exposure and subsequent drug penetration. Because the composition is preservative-free, the ophthalmic composition of the invention avoids the side effects associated with prior art compositions.

5 According to another aspect of the invention, it has further been discovered that calcium plays a key role in the development and maintenance of the preocular tear film and that the delivery of a slowly solubilized, salt of calcium according to the general method of the invention not only  
10 alleviates symptoms of discomfort and dryness, and conjunctival/lid margin redness, but may help correct underlying physical and physiological deficiencies responsible for certain dry eye condition. The delivery of and insoluble calcium salt according to the method of the invention has shown good  
15 effect in alleviating the symptoms of dry for periods of time considerable longer than using conventional deliver systems and with less discomfort to the patient.

These and other objects and advantages of the invention will become more fully apparent after reading the following  
20 detailed description of the invention and examples.

#### Brief Description of the Drawings

FIG. 1 shows in graphic form the effect on intraocular pressure of pilocarpine delivered according to the method of the  
25 invention as described in greater detail for Patient One in Example VIII.

FIG. 2 shows in graphic form the effect on intraocular pressure of pilocarpine delivered according to the method of the invention as described in greater detail for Patient Two in  
30 Example VIII.

Detailed Description of the Invention

According to one aspect of the present invention, a method of topical drug delivery is provided. According to this method, a desired drug is physically mixed with a pharmacologically acceptable carrier. The suitability of the carrier will be dictated both by its pharmacological acceptability for introduction into the eye and by the chemical characteristics of the desired drug. Although the carrier may be selected from a wide variety of compounds such as water-based solutions and gels, it is preferred to provide a carrier that is hydrophobic and that will not readily evaporate when brought into contact with the air. Petrolatum is particularly suitable as such a carrier. Like many of the lipids produced by the Meibomian glands, petrolatum is hydrophobic, will not evaporate, is an excellent solvent for lipids and is an excellent inert and non-interactive with the tissues of the eye and can be obtained in a suitable pure state. Ophthalmological composition based on petrolatum and other water-free compounds is further preferred because it avoids the need for preservative agents.

The type of therapeutic agent or agents to be selected will depend primarily on the disease or disorder to be treated. These agents include a broad array of drugs currently delivered to the eye in topical fashion including, but not limited to, cyclosporine A, vitamin A alcohol, and testosterone, which are used to treat tear disorders: pilocarpine, beta blockers, and carbonic anhydrase inhibitors, which are used for the treatment of glaucoma; and antifungals and antivirals, which are used for the treatment of keratopathies. With regard to preparation of a drug-containing vehicle, it is within the knowledge of one skilled in the art to determine the correct amounts of drug to be added to the appropriate carrier in order to assure the efficacious delivery of the desired drug. It should also be noted that

delivery of the desired therapeutic agent can be extended over time by selected a chemical form of the agent that is somewhat insoluble in water. The greater the insolubility, the longer the agent will take to dissolve and thus come into contact with eye tissue.

In the method of the invention, the drug/vehicle composition is manually placed on the extraocular skin adjacent to the lateral canthus using either one's finger or a suitable applicator, such as a cotton swab. Movements of the orbicularis oculi associated with the scissor-like closing of the lids transports a portion of the composition into the interpalpebral space. The drug is then released by dissolution into the tear film and from there passes into the eye through the corneal tissue. It will be appreciated the amount of composition delivered to the extraocular skin region is not critical because only a small portion of the composition is consumed by each eye blink. The amount of composition to be delivered can depend therefore largely on the period of time desired between applications.

According to another aspect of the present invention, a topical drug comprising a minimally water-soluble, calcium-based composition that may be administered directly to the ocular surfaces or may be administered through the use of ocular inserts or by placing the composition on the skin of the lateral inferior lid margins.

The composition itself is derived from a physical mixture of a poorly water-soluble calcium salt and a pharmacologically acceptable carrier. It is important that the calcium salt be very finely divided, preferably into microfine particles having a mean diameter of 60 microns or less. In one embodiment in which the composition carrier is hydrophobic, The mean particle diameter is 10 to 60 microns. In another embodiment in which

the composition carrier is hydrophilic, the mean particle diameter is 10 microns or less. Division of the calcium salt into microfine particles may be accomplished by any standard means, such as pulverization in a mortar and pestle, or more simply by levigation with the polyol such as glycerol or propylene glycol.

It is also important that the calcium salt be selected be largely insoluble in water. This will ensure a slow release over time of calcium ion into the tear film, thereby obviating the need for continuous or frequent application of the composition.

Suitable calcium salts include calcium carbonate ( $\text{CaCO}_3$ ), calcium tartrate ( $\text{CaC}_4\text{H}_4\text{O}_6$ ), calcium magnesium carbonate ( $\text{CaCO}_3 \cdot \text{MgCO}_3$ ), calcium metasilicate ( $\text{CaSiO}_3$ ), calcium sulfate ( $\text{CaSO}_4$ ), calcium malate ( $\text{Ca}_4\text{H}_4\text{O}_6$ ) secondary calcium orthophosphate ( $\text{CaHPO}_4$ ), and similar poorly water soluble calcium salts that are physiologically compatible and stable. Among these calcium carbonate, with a solubility of 0.0014gm/100ml in cold water, is preferred.

Turning now to the carrier, either hydrophobic or hydrophilic carriers are acceptable, although a hydrophobic carrier is preferred because it tends to be washed from the eye much less quickly than a typical hydrophilic carrier and can be applied to the external to the eye. As described more generally above, the preferred carrier for a drug therapeutic for dry eye is hydrophobic and sufficiently viscous to prevent dripping or running after application. Further, a water-free carrier may preclude the need for preservatives. Such a preferred carrier is petrolatum. The melting point of petrolatum may be increased by the admixture of a suitable substance such as white wax.

Although less preferred, suitable, pharmacologically acceptable, hydrophilic carriers include physiological saline, with or without viscosity enhancing agents to delay wash-out, such as methyl

cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose, polyethyleneoxide, and dextrans, along with any of the artificial tear formulations disclosed in the following United States Patents, the contents 5 of which are herein incorporated by reference: 4,131,651, to Shah, et al.: 4,409,205 to Shively; 4,744,980 and 4,883,658, both to Holly; 55,075,104 to Gressel et al.

It will be apparent that the use of calcium ion to treat dry eye does not necessarily exclude the use of other known 10 therapies. It should be possible to combine the delivery of calcium with that of other known therapies, such as the use of retinoids, estrogens, and the like. However, one must be careful to avoid compositions that include chelating or other binding agents having an affinity for ionic calcium.

15 The composition of the invention may be applied topically to the eye, either directly, indirectly or through the use of an ocular insert. Direct application to the eye surface is best accomplished by instilling a preparation of the composition that has a hydrophilic carrier, such as drops of a saline or artificial tear solution containing a calcium salt.

20 Although the above methods of application are possible, it is preferred to apply the composition extraocularly according to the general method of the invention by placing a small quantity of the composition on the skin adjacent to the lateral 25 canthus. This enables the entrance of small volume of the composition into contact with the fluid in the tear meniscus, and presumably thence into the preocular tear film. Although not wishing to be bound by any theory of operation, it is hypothesized that movement of the composition into the liquid 30 between the interpalpebral space occurs through the interaction of several mechanisms. First, the petrolatum-based vehicle melts at body temperature without evaporating, resulting in a

flow over the lid margin. Transport into the tear meniscus, and ultimately into the tear film, is probably accomplished by movement of the orbicularis orbis muscle of the lower lid during the blink. Although the results of such passage have been shown by the relief of symptoms and signs, evidence of such action has also been gained by the application of the composition containing 6% sodium fluorescein in petrolatum. This soluble salt could be visualized four minutes after application and could be seen up to 40 minutes later. No fluorescence was observed during this interval following the placement of an identical ointment containing fluorescein acid.

The optimal active component is one that is miscible with the hydrophobic vehicle yet is water soluble. More effective action may be obtained from components that are potentially water soluble.

#### EXAMPLES

##### Example I: Preparation of Hydrophobic Composition

The calcium salt is finely divided by any standard means, such as pulverization in a mortar and pestle, or more simply by levigation with a polyol such as glycerol or propylene glycol. The finely divided powder or the polyol mixture is then admixed with a neutral ointment base such as petrolatum. In order to delay release of the calcium ion, substances with a higher melting point, such as white wax may be admixed with the petrolatum to prolong passage of the preparation. A suitable hydrophobic preparation includes 2% to 25% weight by weight of the desired calcium salt.

##### Example II: Preparation of Hydrophilic Composition

The desired calcium salt is first pulverized as described in Example I. Either the finely divided calcium salt or the polyol mixture is then admixed with an appropriate aqueous solution

such as normal saline or a mixture of sodium and potassium chlorides to mimic the ratio in normal tear fluid. The viscosity may be increased to suitable physiological levels by the addition of suitable viscosity increasing agents such as methyl cellulose,  
5 hydroxyethyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose, polyethyleneoxide, and dextrans, along with any of the artificial tear formulations disclosed in the foregoing specification. A suitable hydrophobic preparation includes 0.05% to 5% weight by weight of the desired calcium  
10 salt.

Example III: Treatment Protocol

Hydrophobic preparation

Frequency of use: once or twice daily, and following face  
15 washing.

Length of benefit: 3 hours or longer.

Degree of therapeutic benefit: significant alleviation of dry eye symptoms, including irritation, scratchiness and excessive tearing.

20  
Hydrophilic preparation  
Frequency of use: 3-4 times daily.  
Length of benefit: 2 hours or longer.  
Degree of therapeutic benefit: significant alleviation of dry eye  
25 symptoms, including irritation, scratchiness and excessive tearing.

Example IV: Clinical Findings, Group I

A first group comprised three persons, two female and  
30 one male, ranging in ages from 60 to 70 years. No member of the group was a contact lens wear. The females had keratoconjunctivitis sicca ("KCS") in varying severity, the male

had chronic seborrheic tear film instability. Conventional treatment with tear substitutes provided transient relief at best. To date, all have been successfully treated with daily application of the hydrophobic formulation of Example I for 5 more than four months. There have been no detectable side effects.

Female I had long-standing KCS. She was treated by a single daily application of the hydrophobic formulation of Example I having a 10% weight by weight content of calcium carbonate. The formulation was applied to the skin immediately adjacent to each lateral canthus. Noticeable relief of symptoms occurred within 20 to 30 minutes later. Daily application was followed by complete disappearance of burning, itching, redness and epiphora. Reapplication was necessary on a daily basis and 10 after face washing.

15

Female II had milder KCS than female I, exhibiting no epiphora. She was treated identically as female I. Signs and symptoms of KCS improved markedly following application of the formulation. Re application was necessary on a daily basis 20 and after face washing.

Male I suffered from chronic seborrheic film instability. Male I was treated identically to Female I. After application, visual acuity improved from 20/40 to 20/20 or 20/15. Relief of symptoms was enhanced when the formulation was applied to 25 margin of lower lid morning and at bedtime. Reapplication was necessary on a daily basis and after face washing.

#### Example V: Clinical Findings, Group II

A second patient population comprising 30 individuals 30 ranging in ages from 45 to 88 years was studied. Two members of the group were diabetic, 1 was leukemic. All patients were selected on the basis of being chronic, poorly

responsive to conventional treatments and exhibited clinically obvious signs of tear problems such as bulbar injection and lid redness. Purely objective assessment of improvement was therefore possible from serial photographic records. Patients 5 with tear meniscal widths less than 0.1 mm were excluded.

Each patient was treated with the hydrophobic composition of Example I containing 10% weight by volume of calcium carbonate. The composition was applied daily by the clinic ophthalmologist. Most patients were treated once daily at 10 8:00 am. The severest cases were treated three times a day. The longest course of treatment lasted 8 weeks. All but three patients showed objective and subjective improvement; of these, one did not return and two were discontinued after one week because of lack of objective improvement. Some patients 15 required only once or twice weekly treatment. There were no allergic responses; no condition worsened.

#### Example VI: Effect of Other Divalent Cations

The effect of magnesium, the other main divalent cation 20 in normal tears, on dry eye was studied. A hydrophobic composition according to Example I, containing 10% weight by weight of magnesium carbonate, was tested for its effect on symptoms and signs of dry eye. The composition was administered to each of the patients described in Example IV. 25 No detectable improvement in either signs or symptoms was detected. The same results were obtained in a masked study on these same individuals.

#### Example VIII: Pilocarpine Preparation

A hydrophobic composition containing pilocarpine was 30 prepared according to the following protocol. The pilocarpine is obtained in acidic form as pilocarpine HCl and dissolved in

glycerol. The glycerol-pilocarpine composition is then dispersed in petrolatum in a desired concentration by weight. In order to delay release of the pilocarpine, substances with a higher melting point, such as white wax, may be admixed with the 5 petrolatum to prolong passage of the preparation. A suitable hydrophobic preparation includes 1 - 10% weight by weight of the pilocarpine.

Example VIII: Effect of Pilocarpine Delivery

10 In order to test the efficacy of the extraocular method of topical ophthalmic drug delivery of the presept invention, a 4% pilocarpine ointment was prepared according to the protocol provided in Example VII. Approximately 50 mg of ointment was delivered extraocularly to a position adjacent to the lateral 15 canthus of each patient. IOP and pupil diameter were measured immediately prior to application and at hourly intervals thereafter during the ensuing 18 hours. Patient One was a male 49 years of age. Patient Two was a female 59 years of age.

20 The results for Patient One are shown graphically in FIG. 1. In this patient, pilocarpine was delivered to each eye according to the extraocular delivery method of the invention, and the effect on intraocular pressure followed for a period of 16 hours after administration. The effects of the pilocarpine on 25 the reduction of intraocular pressure can be clearly observed for and extended period, demonstrating the effectiveness of the drug delivery method of the invention.

The results for Patient Two are shown graphically in FIG. 2. The results for Patient Two are shown graphically in FIG. 2 30 Pilocarpine was delivered to Patient Two according to the same protocol used with Patient One. Reduction in intraocular pressure following extraocular application of the pilocarpine

ointment can be clearly observed.

From the foregoing, it can now be appreciated how the objects and features of the invention are met. The method of 5 the invention provides a safe, efficient means of topical delivery of ophthalmologically therapeutic agents over a prolonged period without the need for repetitive reapplication.

The method of the invention is clearly advantageous over the prior art in that extraocular delivery to the lateral canthus 10 provides ease of administration, comfort, improved visual acuity during treatment, probable avoidance of the need for preservative agents in the therapeutic composition, minimal wash out of the therapeutic compound or existing tear film, minimal transconjunctival loss of drug delivery to the optimal 15 area for absorption, as well as minimal absorption across the conjunctiva.

According to another aspect of the invention, the method of the invention can be used to deliver a calcium-containing ointment to provide a ready source of calcium ion to the ocular 20 surface. Because the ionic calcium is derived from a calcium salt that is minimally soluble in water, slow, long term release of ionic calcium into the tear film is effected.

The invention is clearly advantageous over known treatments in that long term relief of symptoms can be achieved 25 with a minimum number of applications, generally once daily. Presently available dry eye treatments have durations of effectiveness that can be measured in mere minutes. According to Lemp (1972), the actual retention time of instilled artificial tears is in order of minutes, a period inadequate to provide 30 comfort for the severe dry eye patient. This situation has not significantly changed in the ensuing years.

The invention is generally advantageous in

its ease of administration. The administration of conventional ophthalmic therapeutic preparations poses a problem especially for the older presbyopic patient. Proper placement of either drops or ointment without self-inflicted ocular injury can be difficult even to the normal sighted, requiring positional gymnastics and a steady hand. In contrast, the extraocular application at lid margins avoids the potential for injury that may result from delivery of therapeutic agents directly to the ocular surface.

10        Although the invention has been described with respect to a particular method of extraocular topical application of therapeutic agents and with regard to a specific calcium-bearing composition for treating dry eye syndrome, it will be appreciated that various modifications of the composition and  
15      method are possible without departing from the invention, which is defined by the claims set forth below.

I claim:

1. A calcium-based ophthalmic composition for treatment of dry eye syndrome consisting essentially of:

5           a) an ophthalmologically acceptable carrier having a sufficient viscosity to prevent running or dripping of the carrier when the carrier is applied to a more or less vertically oriented surface; and

10          b) dispersed within said ophthalmologically acceptable carrier, a minimally water-soluble, ophthalmologically acceptable salt of calcium selected from the group consisting of calcium carbonate, calcium tartrate, calcium magnesium carbonate, calcium metasilicate, calcium sulfate, calcium malate and secondary calcium orthophosphate, said calcium salt finely divided into particles having a mean diameter of from 10 to 60 microns.

20          2. The composition of claim 1 wherein said ophthalmologically acceptable carrier is hydrophobic.

25          3. The composition of claim 2 wherein said ophthalmologically acceptable carrier is petrolatum.

4. The composition of claim 1 wherein said ophthalmologically acceptable calcium salt is calcium carbonate.

30          5. The composition of claim 1 wherein said ophthalmologically acceptable calcium salt is divided into particles having a mean diameter of 10 microns or less.

6. A calcium-based ophthalmic composition for treatment of dry eye syndrome consisting essentially of:

a) an ophthalmologically acceptable grade of petrolatum; and

5 b) dispersed within said petrolatum, an ophthalmologically acceptable grade of calcium carbonate, said calcium carbonate finely divided into particles having a mean diameter of from 10 to 60 microns.

7. A method for treating a patient afflicted with dry eye comprising the steps of:

10 a) providing a calcium-based ophthalmic composition comprising [applying] a finely divided, minimally water-soluble, ophthalmologically acceptable calcium salt suspended in a ophthalmologically acceptable carrier; and

15 b) applying said calcium-based ophthalmic composition adjacent to lateral or inferior lid margins exterior to an ocular surface,

20 wherein blinking action of the lid margins cuts off and carries the composition into contact with the ocular surface in amounts and for time sufficient to effect treatment of the dry eye condition.

8. A method of treating a patient afflicted with dry eye comprising the step of:

25 a) providing a calcium-based ophthalmic composition consisting essentially of a finely divided, ophthalmologically acceptable grade of calcium carbonate suspended in a ophthalmologically acceptable grade of petrolatum; and

30 b) applying said calcium-based ophthalmic composition adjacent to lateral or inferior lid margins exterior to an ocular surface,

wherein blinking action of the lid margins cuts off and carries the composition into contact with the ocular surface in amounts and for time sufficient to effect treatment of the dry eye condition.

5

9. A method for treating a patient afflicted with dry eye comprising the steps of:

- a) providing a calcium-based ophthalmic composition comprising a finely divided, minimally water-soluble, ophthalmologically acceptable calcium salt suspended in an ophthalmologically acceptable hydrophobic carrier, wherein said calcium salt is divided into particles having a mean diameter of 10 to 60 microns; and
- b) applying said calcium-based ophthalmic composition adjacent to the lateral or inferior lid margins exterior to an ocular surface,

wherein blinking action of the lid margins cuts off and carries the composition into contact with the ocular surface in amounts and for time sufficient to effect treatment of the dry eye condition.

10. A method for treating a patient afflicted with dry eye comprising the steps of:

- a) providing a calcium-based ophthalmic composition comprising a finely divided, minimally water-soluble, ophthalmologically acceptable calcium salt suspended in petrolatum, wherein said calcium salt is divided into particles having a mean diameter of 10 to 60 microns; and
- b) applying said calcium-based ophthalmic composition adjacent to the lateral or inferior lid margins exterior to an ocular surface,

wherein blinking action of the lid margins cuts off and carries the composition into contact with the ocular surface in amounts and for time sufficient to effect treatment of the dry eye condition.

5

11. A method of delivering one or more therapeutic agents to a corneal surface of a human eye for the treatment and/or prevention of human ophthalmic diseases, said method comprising:

- 10        a) providing an ophthalmological composition comprising an ophthalmologically acceptable carrier and a therapeutically effective dose of one or more therapeutic agents combined with the carrier;
- 15        b) applying said ophthalmological composition to an adjacent to the lateral or inferior lid margins exterior to an ocular surface,

20        wherein blinking action of the lid margins cuts off and brings into contact with the ocular surface said composition in sufficient amounts and for sufficient time to effect treatment or prevention of the human ophthalmological disease.

25        12. The method according to claim 11 wherein the ophthalmologically acceptable carrier is hydrophobic and has a viscosity sufficient to prevent said composition from running or dripping after said composition is applied.

30        13. The method according to claim 12 wherein the ophthalmologically acceptable carrier comprises petrolatum.

14. The method according to claim 11 wherein the one or more therapeutic agents is selected from the group

**consisting of calcium salts, retinoids, testosterone, estrogen and its derivatives, anti-bacterial agents, anti-viral agents, anti-fungal agents, vitamin A alcohol, beta blockers and carbonic anhydrase inhibitors.**

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INTRAOCULAR PRESSURE (mm Hg)

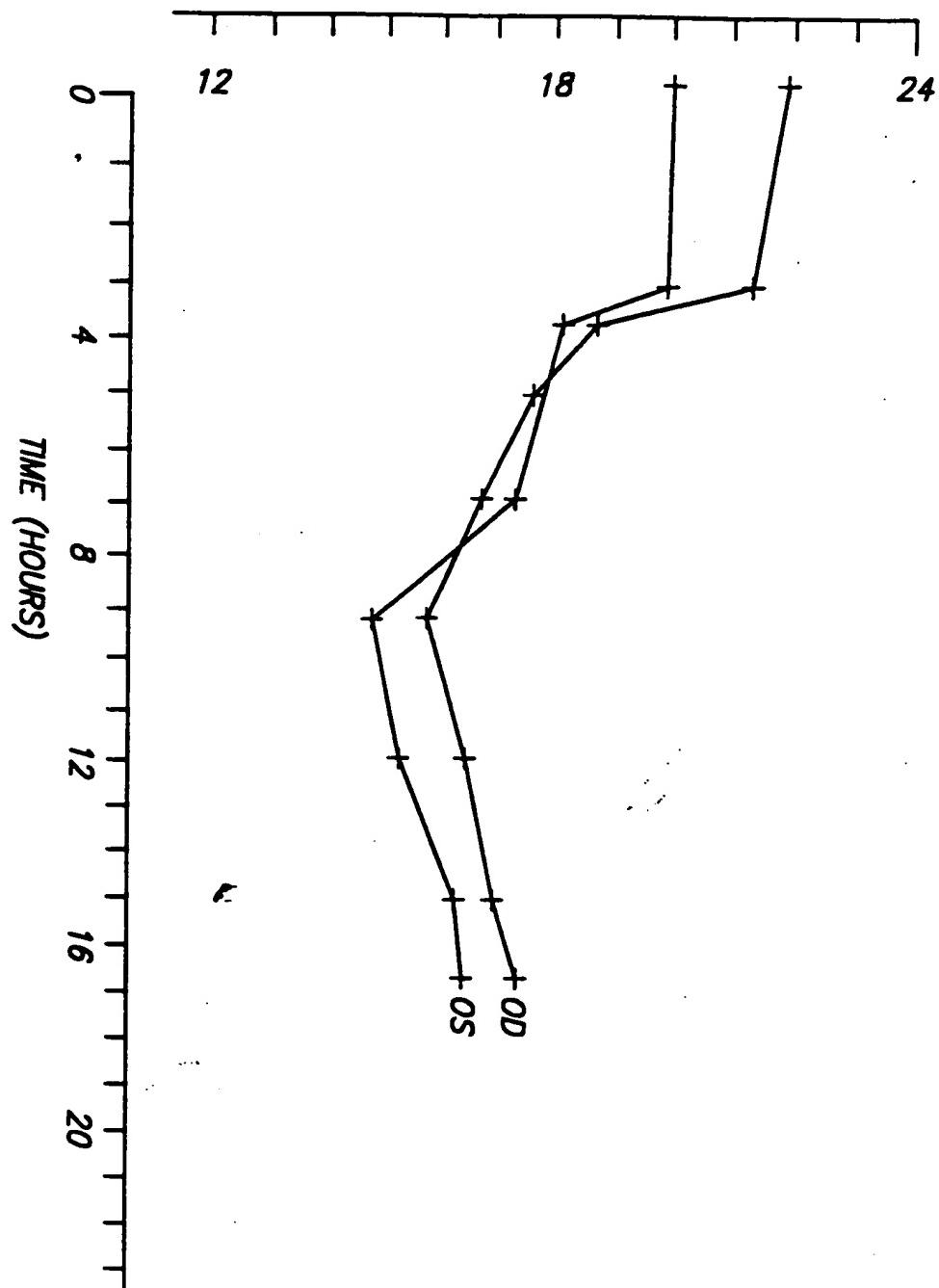


FIG. 1

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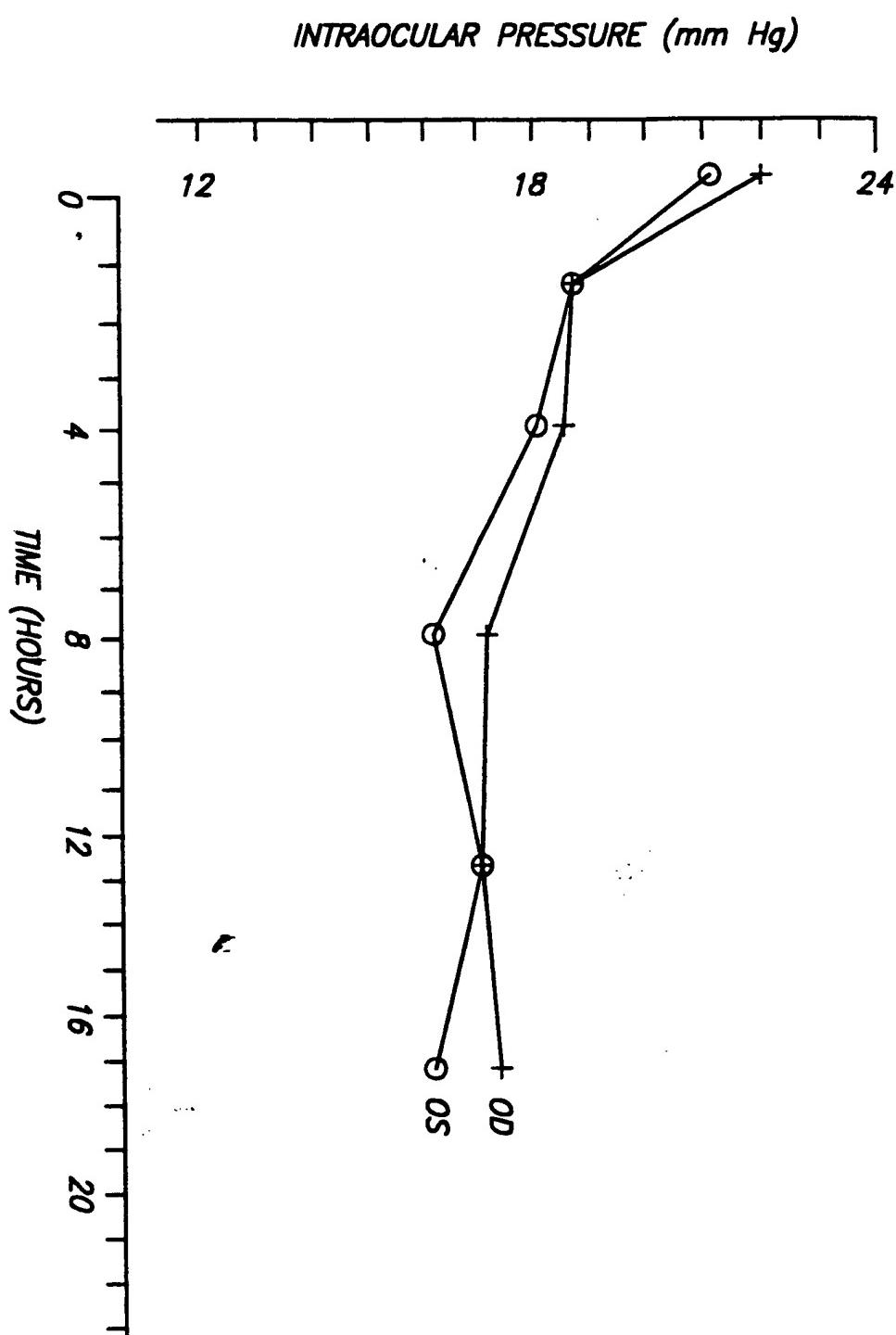


FIG. 2

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## INTERNATIONAL SEARCH REPORT

In national application No.  
PCT/US93/11873

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(5) : A61K 33/42, 33/10, 33/06  
US CL : 424/602, 603, 687, 696; 514/912

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/602, 603, 687, 696; 514/912

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Dialog

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	"Physicians' Desk Reference for Ophthalmology", published 1988 by Edward R. Barnhart. See pages 13, 153	1-14
Y	Product Alert, Volume 21, issued 28 October 1991, "Bausch & Lomb Dry eye therapy lubricating eye drops manufacture". See the abstract 1261920 document.	1-14

Further documents are listed in the continuation of Box C.

See patent family annex.

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•a•	document number of the same patent family

Date of the actual completion of the international search

16 FEBRUARY 1994

Date of mailing of the international search report

MAR 28 1994

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